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REMARKS

Applicant acknowledges the current status of the claims, as reported in Office Action dated 10 August 2007. Claims 1-20 are pending; claims 8-20 are withdrawn from consideration; and claims 1-7 are under consideration. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Specification

In the office action at page 2, the Examiner has requested the Applicant to determine whether materials incorporated by reference are essential or non-essential, and amend the specification accordingly. Applicant requests the Examiner to hold this requirement in abeyance until final disposition and allowance of claims in the present application.

Rejections under 35 USC §103(a)

In the Office Action, at page 3, claims 1-7 are rejected again under 35 USC §103(a) as being unpatentable over WO 00/34317 A2 in view of US 20050191706 A1. The Examiner continues to assert that it would be obvious to one skilled in the art to combine the teachings of WO 00/34317 A2 and US 20050191706 A1 to arrive at Applicants' invention. Applicants respectfully disagree.

BASIC REQUIREMENTS OF A *PRIMA FACIE* CASE OF OBVIOUSNESS

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations.
>
> MPEP §2143

It is well recognized that:

> Hindsight reconstruction of a claimed invention, absent a teaching or suggestion in the art is impermissible.
>
> MPEP §2142

Applicant's invention is directed to a method for detecting a deantigenized T cell epitope by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule. In an additional embodiment the method for detecting a deantigenized T cell epitope further comprises the steps of: (e) providing one or more altered T cell epitopes, wherein the amino acid sequence of the one or more altered T cell epitopes is different from the amino acid sequence of a deantigenized T cell epitope obtained in step (d); and (f) repeating steps (c) and (d) above.

The PCT publication, WO 00/34317 A2, teaches a method of altering potential T cell epitopes within the protein to eliminate potential epitopes (see page 7, lines 6-8). As stated in the paragraph spanning page 8-9, "A typical protocol within the general method of the present invention comprises the following steps: I. Determining the amino acid sequence of the protein or a part thereof (if modification only of a part is required); II. Identifying potential T cell epitopes within the amino acid sequence of the protein by any method including determination of the binding of peptides to MHC molecules, determination of the binding of peptide:NMC complexes to the T cell receptors from the species to receive the therapeutic protein, testing of the protein or peptide parts thereof using transgenic animals with the MHC molecules of the species to receive the therapeutic protein, or testing with transgenic animals reconstituted with immune system cells from the species to receive the therapeutic protein; III. By genetic engineering or other methods for producing modified proteins, altering the protein to remove one or more of the potential T cell epitopes and producing such an altered protein for testing; IV. (optionally) Within step III., altering the protein to remove one or more of the potential B cell epitopes; V. Testing altered proteins with one or more potential T cell epitopes (and optionally B cell epitopes) removed in order to identify a modified protein which has retained all or part of its desired activity but which has lost one or more T cell epitopes."

The PCT publication WO 00/34317 A2, does not teach or suggest Applicant's method for detecting a deantigenized T cell epitope by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for

sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule. As stated on page 3 of Applicant's specification, " The present invention provides a novel method for detecting a deantigenized T cell epitope. Described herein for the first time is a method for detecting a deantigenized T cell epitope, which method employs a cell solubilized or genetically produced MHC molecule ("soluble MHC" or "sMHC") for peptide screening and binding assays. Although use of some sMHC assays to screen for peptides that induce or increase cytotoxic T lymphocyte (CTL) responses compared to a parental peptide have been described (i.e., Vitiello et al., 2001, describe hepatitis B virus surface and nucleocapsid peptide antigens with increased MHC class I-restricted CTL-stimulating properties), use of a sMHC assay to detect modified T cell epitopes having reduced or no immunogenicity (via a binding affinity to a MHC molecule less than the binding affinity of a given parental or template T cell epitope to that MHC molecule) is first contemplated and reduced to practice by the Applicant as described herein." The PCT publication WO 00/34317 A2 does not disclose an sMHC assay to detect modified T cell epitopes having reduced or no immunogenicity. In addition, WO 00/34317 A2 teaches altering one or more T cell epitopes in the protein of interest and assaying the altered protein for reduction in immunogenicity, and not Applicant's method of providing one or more altered T cell epitopes and comparing their binding in an sMHC assay in comparison to the T cell epitope to detect a deantigenized T cell epitope.

US 20050191706 A1 discloses that the typical dissociation constant between a peptide antigen and an MHC molecule ranges from micromolar to nanomolar range. The Examiner asserts that although PCT publication WO 00/34317 A2 does not teach that the deantigenized T cell epitope produced by the art method possesses the property of having a dissociation constant with the soluble MHC molecule greater than or equal to about 5×10^{-7} M; 5×10^{-5} M; or 5×10^{-3} M; the art method appears to produce a deantigenized T cell epitope having said dissociation constant as evidenced by US 20050191706 A1. Applicant respectfully submits, that for reasons stated above, PCT publication WO 00/34317 does not teach or suggest Applicant's claimed method. Despite the disclosure in US 20050191706 A1 that dissociation constant between a peptide antigen and an MHC molecule ranges from micromolar to nanomolar range, the fact is PCT publication WO 00/34317 does not teach or suggest Applicant's claimed method, and thus not meet the third requirement for a *prima facie* case of obviousness.

Since PCT publication WO 00/34317 A2 does not teach or suggest each and every element of the present invention either expressly or inherently; either singularly or in combination with US 20050191706 A1, the cited references fail to render Applicant's invention obvious.

Because the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 1-7 as obvious under 35 USC §103(a), and in view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 1-7 under 35 USC §103(a).

In the Office Action, at page 4, and again at page 6 claims 1-7 are rejected under 35 USC §103(a) as being unpatentable over US 2002/0119492 A1 in view of DiBrino et al., (J. Immunol. 1993, 151(11):5930-5935) and US 20050063983. The Examiner continues to assert that it would be obvious to one skilled in the art to combine the teachings of US 2002/0119492 A1 in view of DiBrino et al., (J. Immunol. 1993, 151(11):5930-5935) and US 20050063983 and arrive at Applicant's invention. Applicant respectfully disagrees.

Applicant's invention is directed to a method for detecting a deantigenized T cell epitope by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule. In an additional embodiment the method for detecting a deantigenized T cell epitope further comprises the steps of: (e) providing one or more altered T cell epitopes, wherein the amino acid sequence of the one or more altered T cell epitopes is different from the amino acid sequence of a deantigenized T cell epitope obtained in step (d); and (f) repeating steps (c) and (d) above.

As acknowledged by the Examiner, US Patent Publication 2002/0119492 A1 discloses a method of modulating the immunogenicity of a target protein by using computational methods to identify variant proteins, generating a set of variant proteins and testing them for immunogenicity, but does not teach or suggest Applicant's method for detecting a deantigenized T cell epitope by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule.

DiBrino et al., (J. Immunol. 1993, 151(11):5930-5935) teach a peptide binding assay using soluble MHC class I molecule to identify immunogenic peptide epitopes from influenza viral proteins. DiBrino et al., (J. Immunol. 1993, 151(11):5930-5935) do not teach or suggest Applicant's method for detecting a **deantigenized T cell epitope** by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule. Further DiBrino et al., **do not teach or suggest the use of a sMHC assay** to detect modified T cell epitopes having reduced or no immunogenicity (via a binding affinity to a MHC molecule less than the binding affinity of a given parental or template T cell epitope to that MHC molecule).

US Patent Publication 20050063983 discloses peptides from HBV that bind MHC class I molecules. US Patent Publication 20050063983 does not teach or suggest Applicant's method for detecting a deantigenized T cell epitope by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule.

The Examiner continues to assert that it would have been obvious to one skilled in the art to combine the cited references to arrive at Applicant's invention. The Examiner has used Applicant's disclosure as a template to search and reconstruct Applicant's invention. In one aspect, the Examiner has searched for, and subsequently cited US Patent Publication 2002/0119492 A1 as disclosing a computational method to generate variant proteins to test for immunogenicity. In a separate aspect, the Examiner has searched for and cited DiBrino et al., as disclosing a peptide binding assay using soluble MHC class I molecule to identify immunogenic peptide epitopes. In yet another aspect, the Examiner has searched for and cited US Patent Publication 20050063983, which discloses peptides from HBV that bind MHC class I molecules with high affinity. Neither US Patent Publication 2002/0119492 A1, nor

DiBrino et al., teach or suggest the use of sMHC assay to detect modified T cell epitopes having reduced or no immunogenicity. The combination of the cited art is made only by the Examiner, upon guidance, direction, and motivation to do so by Applicants' present invention. This is hindsight reconstruction and is impermissible as a basis for rejection under 35 USC §103.

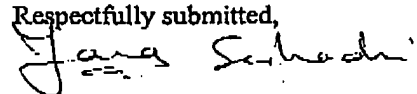
Applicants again assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to arrive at Applicant's method for detecting a deantigenized T cell epitope by; (a) providing an amino acid sequence of a T cell epitope having a binding affinity to a soluble MHC molecule; (b) providing one or more altered T cell epitopes, wherein the amino acid sequence of the altered T cell epitope is different from the amino acid sequence of the T cell epitope; (c) contacting the altered T cell epitope with the soluble MHC molecule for sufficient time to permit MHC-epitope binding complexes to form; and (d) detecting one or more altered T cell epitopes, wherein the detected altered T cell epitope identifies a deantigenized T cell epitope having a binding affinity to the soluble MHC molecule less than the binding affinity of the T cell epitope to the soluble MHC molecule. Instead, the Examiner has employed impermissible hindsight to fabricate a case of obviousness.

Because the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 1-7 as obvious under 35 USC §103(a), and in view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 1-7 under 35 USC §103(a).

Conclusion

In view of the foregoing amendments and remarks, Applicants believe that all objections and rejections set forth in the Office Action of 10 August 2007 have been avoided or overcome, and consequently the application is in condition for allowance. Reconsideration and removal of the rejections, and allowance of the pending amended claims are, therefore, respectfully requested.

Respectfully submitted,



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